

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-640

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

(b) 8 pages have been purged

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-640 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: August 5, 2003 Action Date: May 5, 2004

HFD-550 Trade and generic names/dosage form: Vitrax (hyaluronidase for injection)

Applicant: ISTA Pharmaceuticals, Inc. Therapeutic Class: 3 - new formulation

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Vitrax is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

xNo: Please check all that apply: ☐ Partial Waiver ☐ Deferred ☒ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 16 Tanner Stage _____

Comments: The action letter issued on May 5, 2004 with the 'studies are waived' language at the decision of the ODEV Office. Hyaluronidase was permitted in 1947 and efficacy was re-confirmed in 1970 in a DESI review for a number of indications, including for use in neonates for hypodermoclysis. More information is included in the original Clinical review of 12/8/03 and Summary reviews of the Deputy Director & Acting Division Director of 5/5/04.

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

Lori Marie Gorski

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-640

HFD-960/ Grace Carmouze

(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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/s/

Lori Gorski
5/10/04 03:55:59 PM

**Office Director Memorandum
Office of Drug Evaluation V
Office of New Drugs**

Re: NDA 21-640

Date: May 5, 2004

Sponsor: ISTA Pharmaceuticals, Inc

Proposed Tradename: Vitrase, Lyophilized Ovine (hyaluronidase for injection)

Drug Product: hyaluronidase for injection, lyophilized ovine

Pharmacologic Category: proteolytic enzyme

Proposed Indication: Vitrase® (hyaluronidase for injection) lyophilized, ovine is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

This provides for my concurrence with the recommended approval action discussed in the Division Director memo of Dr. Harvey for this application.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Jonca Bull
5/5/04 03:32:51 PM
MEDICAL OFFICER

Acting Division Director DAAODP/
Deputy Office Director Memorandum
Office of Drug Evaluation V
Office of New Drugs

NDA 21-640

Date: May 5, 2004

Sponsor: ISTA Pharmaceuticals, Inc

Drug Product: Vitrase® (hyaluronidase for injection) Lyophilized, Ovine

Pharmacologic Category: proteolytic enzyme

Proposed Tradename: Vitrase®

Proposed Indication: Vitrase® (hyaluronidase for injection) is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

Background

NDA 21-640 for Vitrase® (hyaluronidase for injection) Lyophilized, Ovine, is a proteolytic enzyme obtained from sheep testes. The hyaluronidases are a family of 1-4 endoglucosaminidases that depolymerize hyaluronic acid (HA) and chondroitin sulfate. These drug products are partially purified preparations usually obtained from mammalian testicular tissue. The family of hyaluronidase products has never been fully characterized.

This specific NDA was submitted as a 505(b)(2) application based on literature and the agency's prior finding of safety and efficacy for the proposed indications approved under the Drug Efficacy and Safety (DESI) review published in the Federal Register September 23, 1970. There is a long history dating to the 1940's of marketing of this drug product. Wyeth's NDA 06-343 was the last remaining marketed NDA approved under the DESI notice. Their hyaluronidase ceased to be marketed due to a business decision by Wyeth Pharmaceuticals in 2002 to stop manufacturing the product. Due to this business decision, hyaluronidase for injection is currently under drug shortage.

Clinical

In general, sodium hyaluronidase is administered in combination with a second drug product. In these situations, hyaluronidase is used as an adjuvant to increase the absorption and dispersion of the co-administered drug product. The mechanism of action of the hyaluronidase is to produce hydrolysis of hyaluronic acid (HA), a viscous mucopolysaccharide which binds water in the interstitial tissues. The clinical efficacy of hyaluronidase is based on its ability to depolymerize HA in tissue, allowing the

co-administered product to flow into that tissue. The USP assay for the assessment of hyaluronidase potency is an *in vitro* measurement of its ability to depolymerize HA.

As outlined in the primary medical review, hyaluronidase for injection has been safely marketed for over 50 years with millions of uses per year. The safety of this product is supported by the DESI evaluation for use as an adjuvant to increase the absorption and dispersion of other injected drugs, for hypodermoclysis, and as an adjunct in performing subcutaneous urography for improving resorption of radiopaque agents. The review of this NDA did not raise any new safety concerns with the use of this product or relevant adverse events that had not been previously included in the product labeling. The most serious labeled adverse events have been hypersensitivity reactions, which have included anaphylactic-like reactions. In several large published series, the frequency of reported events has been less than 0.1%. The more severe events occur even less frequently. Hyaluronidase is not traditionally used intravenously since it is inactivated by the constituents found in blood. It has been recommended that it should not be used on the cornea of the eye because the structural changes produced by hyaluronidase are not predictable.

Due to the reported history of rare hypersensitivity reactions, a consult was obtained from the Division of Pulmonary Drug Products. The following recommendations for hyaluronidase products were provided:

In this circumstance, it may be necessary to conduct an open-label study large enough to rule out a frequency of serious immediate hypersensitivity reactions of 0.5 to 1.0%. All patients should be skin tested prior to administration of the product and serum should be drawn at baseline prior to treatment and frozen. The frequency of immediate hypersensitivity reactions should be assessed and patients who have immediate hypersensitivity reactions should be re-skin tested at a reasonable time after the reaction, perhaps within 1 to 2 months.

Based upon these recommendations, the sponsor conducted a study with their product and reported no hypersensitivity reactions in the study group of 65 patients. Given these results and the supporting published literature, the Clinical Team has recommended that this NDA be approved.

Chemistry and Manufacturing

There are currently no unresolved CMC issues and the Chemistry Team has recommended that this NDA be approved.

Special Populations

The results of clinical trials conducted in the pediatric population have been published and were included in the DESI review. The sponsor appears to be in compliance with the Pediatric Research Equity Act of 2003 (PREA).

Labeling

I agree with the final proposed product label negotiated with the sponsor, including the designation of this product in Pregnancy Category C.

Recommendation

I recommend approval of NDA 21-640 with the product labeling submitted May 5, 2004. This NDA application supports the safety and efficacy of Vitrase® (hyaluronidase for injection), Lyophilized, Ovine for the indication of an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

Brian E. Harvey, M.D., Ph.D.
Acting Director, DAAODP
Deputy Director, Office of Drug Evaluation V
Office of New Drugs
Center for Drug Evaluation and Research

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/s/

Brian Harvey
5/5/04 03:27:12 PM
MEDICAL OFFICER

Deputy Division Director Summary of NDA 21-640

Review completed: May 5, 2004

Proposed Name: Vitrase (hyaluronidase for injection)

Applicant: ISTA Pharmaceuticals
15279 Alton Parkway
Suite 100
Irvine, California, 92618

I. Recommendations

A. Recommendation on Approvability

I concur with the Medical Officer Review recommendations for NDA 21-640 and recommend approval of NDA 21-640.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

No additional Phase 4 studies are recommended. There are no additional recommended risk management steps for this product.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Vitrane (hyaluronidase for injection) — USP units/vial is a protein enzyme prepared from ovine testicular tissue. It is administered as an injection, but is not intended for intravenous use. The efficacy of hyaluronidase for the proposed indications (as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents) is supported by the USP monograph test for hyaluronidase units as a surrogate for hyaluronidase's effect in tissues. The safety and efficacy of hyaluronidase is supported by the DESI evaluation for use published in 1970. Additional safety information for this particular formulation is provided in the clinical safety study conducted by the applicant.

B. Efficacy

The efficacy is supported by the USP test for units of hyaluronidase and the DESI evaluations of hyaluronidase (mammalian origin) (DESI 6343, 6714, 7933) for use as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. There are no unresolved efficacy issues.

C. Safety

Hyaluronidase injection and hyaluronidase for injection have been safely marketed for over 50 years with millions of uses per year. The safety is supported by the literature and the safety study conducted by the applicant which demonstrates an allergic reaction level of less than 10%.

D. Chemistry/Manufacturing Review

I agree with the Chemistry/Manufacturing Review recommendation that the application be approved. The application cross references NDA 21-414, which contains the information necessary to conclude that the applicant is capable of producing a consistent drug product with a definable number of hyaluronidase units as described in the USP monograph.

E. Pharmacology/Toxicology Review

I concur with the Pharmacology/Toxicology conclusions concerning the adequacy of the DESI Review to support the safety and efficacy of the proposed indications. The original Pharmacology/Toxicology Review recommends labeling that include a Pregnancy Category C because there were no reproductive toxicity studies performed by the sponsor. The addendum Pharmacology/Toxicology Memo defers the Pregnancy Category portion of the labeling to the Clinical Review. The Clinical Review recommends a Pregnancy Category —based on the conclusion that adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy and there is no evidence of a risk in later trimesters.

The original publications from the 1950s included reports of the clinical use of hyaluronidase for the treatment of infertility. [Britton RC, Habif DV. Clinical Uses of Hyaluronidase. Recent Advances in Surgery. 1952. 33(6): 917-942.] Included are reports of 4 clinical studies for the treatment of infertility, none of which was statistically significant. One study demonstrated a non-statistically significant conception rate of 26% in 158 treated patients compared to 10% of 157 controls. [Kurzrok R. Ann New York Acad Sc. 1950; 52:1180]. Three other studies demonstrating no effectiveness were reported by Tafel RE, Titus P and Wrightman. 1948; 55:1023. Sallman R in the discussion of the paper by Kurzrok and Siegler SL at the Third Annual Convention of the American Society for the Study of Fertility. While the controlled studies reported no efficacy, there were also no safety problems. Additionally, Kurzrok et al have reported case series in the American Journal of Medicine. Role of Hyaluronidase in Human Infertility. 1946; 1:491-506.

Non-clinical studies evaluating the reproduction toxicity of hyaluronidase include published reports such as Human Reproduction. 1998 Jul;13(7):1933-5 and J Assist Reprod Genet. 1997 Feb;14(2):97-101.

Published clinical studies in the 1st trimester include: *Human Reproduction* 1997 Oct;12(10):2246-50. Effects of different hyaluronidase concentrations and mechanical procedures for cumulus cell removal on the outcome of intracytoplasmic sperm injection. Van de Velde H, Nagy ZP, Joris H, De Vos A, Van Steirteghem AC. Centre for Reproductive Medicine, Dutch-speaking Brussels Free University (Vrije Universiteit Brussel), Belgium and J In Vitro Fert Embryo Transf. 1988 Oct;5(5):257-60. Published clinical studies in the 3rd trimester include: *Chin Med J (Engl)*. 1994 Jul;107(7):552-3. Effect of hyaluronidase on cervical ripening. Li WJ, Li ZL, Ha KW. Department of Obstetrics and Gynecology, Union Hospital, Tongji Medical University, Wuhan. *American Journal of Obstetrics & Gynecology*. 1967. 99(3): 337-340. Intracervical injection of hyaluronidase. Green, PS. Department of Obstetrics and Gynecology, Newark City Hospital, Newark, NJ. *Obstetrics and Gynecology*. 1965. 26(1): 66-69. Hyaluronidase in Episiotomy. OLeary JA and Erez S. Department of Obstetrics and Gynecology, Sloane Hospital for Women, Columbia-Presbyterian Medical Center, NY, NY.

A decision was made to label the product as Pregnancy Category C because the animal studies were not conducted under Good Laboratory Practices (GLP) and the human studies do not have long term follow-up of the children.

F. Pediatrics

Clinical studies have been conducted in pediatric patients and included in the DESI review. Published studies include:

Schwartzman J and Levbarg M. Hyaluronidase: Further Evaluation in Pediatrics. *The Journal of Pediatrics*. 1950; 36: 79-86.

Britton RC, Habif DV. Clinical Uses of Hyaluronidase. *Recent Advances in Surgery*. 1952. 33(6): 917-942.

G. Trademark

DDMAC and DMETS were consulted with respect to the trademark, Vitrase. DDMAC had no objection to the trademark. DMETS after review of DAAODP comments, agreed that the potential for confusion with Vitrasert and Vitravene was low, but remained concerned over potential confusion with AMO Vitrax. Vitrax is sodium hyaluronate and is approved as a medical device. DAAODP considers the potential for confusion to be low because prescriptions are not written for either product, the dosage forms are different, and the packaging is not compatible with instructions for administration of the mistaken product (cannule versus needle for injection). DAAODP has taken into consideration the labeling comments in DMETS recommended labeling revisions. Based on comments from DAAODP and ODEV, revised labeling has been suggested to the applicant.

H. Labeling

The entire labeling was re-reviewed by the entire review team including members of the immediate ODE V on May 4, 2004. The following changes listed below with underline or strikeout have been proposed:

Vitrase
(hyaluronidase for injection)
Lyophilized, Ovine

DESCRIPTION

5 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

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/s/

Wiley Chambers
5/5/04 11:49:47 AM
MEDICAL OFFICER

Wiley Chambers
5/5/04 11:52:37 AM
MEDICAL OFFICER

Memorandum

From: Zhou Chen
Through: Josie Yang
To: Lori Gorski
Date: May 4, 2004
Re: NDA 21-640 Labeling Review
Vitrase
ISTA Pharmaceuticals, Inc.

The following changes in the labeling for NDA 21-640 are made following discussion during the team meeting on May 4, 2004.

1. In the "CLINICAL PHARMACOLOGY" section, two paragraphs referring findings from animal studies (see below) are removed. These animal studies were not conducted with Vitrase for this NDA submission, and did not provide additional information on clinical pharmacology.

2. In the "PRECAUTIONS" section, the second sentence under the "Carcinogenesis, mutagenesis, impairment of fertility" subsection was removed (see below) as suggested by Dr. Abigail Jacobs, Pharmacology/Toxicology Associate Director for ODE4/5. The study results were not from this NDA submission and it is not appropriate to place this information under the section of "Carcinogenesis, mutagenesis, impairment of fertility".

3. The "Teratogenic Effects—Pregnancy Category" under the "Pregnancy" section will be "C" as indicated in the original pharmacology/toxicology review. However, this section is revised as followings: "No adequate and well controlled animal studies have been conducted with Vitrase to determine reproductive effects. No adequate and well controlled studies have been conducted with Vitrase in pregnant women. Vitrase should be used during pregnancy only if clearly needed."

cc: list:

NDA 21-640/Division File
NDA 21-640/Original NDA
HFD-550/CSO/Gorski
HFD-550/MO/Harris
HFD-550/TL Pharm/YangJ
HFD-550/Pharm/ChenZh
HFD-540/AD Pharm/JacobsA

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/s/

Zhou Chen
5/4/04 05:04:32 PM
PHARMACOLOGIST

Josie Yang
5/4/04 05:17:58 PM
PHARMACOLOGIST

Memorandum

From: Zhou Chen
Through: Josie Yang
Date: April 22, 2004
Re: NDA 21-640
Vitrase
ISTA Pharmaceuticals, Inc.

No reproductive toxicity studies were performed by the sponsor. There are no reports of any GLP reproductive toxicity studies on embryo-fetal and post-natal development conducted with exogenous hyaluronidase parenterally. It is difficult to conduct reproduction toxicity studies with foreign proteins in rats and rabbits as allergic, or moreover, anaphylactic response may occur. In addition, at doses high enough, certain embryo-fetal developmental effects may be seen based on the mechanisms of action of the drug. Based on the limited nonclinical information, the reviewer concurred with the sponsor's decision in the labeling, Pregnancy Category C.

On the other hand, the drug has been marketed for many years and has been generally considered as safe and well tolerated. If adequate and well-controlled clinical studies in pregnant women with mammalian hyaluronidase have failed to show any risk to the fetus in the first trimester and there is no evidence of any risk on later trimesters or any effects on reproduction capacity [21 CFR 201.57 (f)(6)(i)(a)], then clinical data can supersede nonclinical data. In this case, the final decision regarding the labeling is a medical judgmental call and is deferred to the clinical reviewer.

cc: list:

NDA 21-640/Division File
NDA 21-640/Original NDA
HFD-550/CSO/Gorski
HFD-550/MO/Harris
HFD-550/TL Pharm/YangJ
HFD-550/Pharm/ChenZh

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/s/

Zhou Chen
4/22/04 01:39:31 PM
PHARMACOLOGIST

Josie Yang
4/23/04 09:11:19 AM
PHARMACOLOGIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 20, 2004

FROM: William Boyd, M.D.
Clinical Team Leader
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

THROUGH: Wiley Chambers, MD
Deputy Division Director, HFD-550
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

THROUGH: Brian Harvey, M.D., Ph.D.
Acting Division Director, HFD-550
Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products

TO: Jonca Bull, M.D.
Office Director, HFD-550
Office of Drug Evaluation V

SUBJECT: Intradermal Injections of Hyaluronidase

The original test for the allergenicity of hyaluronidase was arbitrarily — of the proposed drug product. The product originally on the market was 15 units of hyaluronidase; therefore the test was 1.5 units. This testing was adequate to elicit allergic reactions in susceptible patients.

The next version of the product packaging was 30 units, and the recommended intradermal skin test became 3 units. This was written into the labeling of the hyaluronidase products. Later, products became packaged as 150 units or 1500 units per mL.

The Division initially suggested a volume of 0.1 mL for the convenience of administration; sponsors have preferred to utilize 0.02 mL of a 150 units/mL solution even though it is more difficult to withdraw and administer (i.e. requires a special size syringe).

This 0.02 mL volume for intradermal injection is acceptable. Historically, any amount of hyaluronidase ≥ 1.5 units will give a reaction if a patient is allergic.

Cc:

NDA 21-665

NDA 21-640

NDA 21-716

NDA 21-593

ODEV/Dir/Bull

ODEV/ADRA/Rumble

HFD-550/Sup CSO/DeBellas

HFD-550/Div Dir/Harvey

HFD-550/Dep Div Dir/Chambers

HFD-550/CSO/Gorski

HFD-550/CSO/Puglisi

HFD-550/M.O./Harris

HFD-550/M.O./Lim

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/s/

William Boyd
4/20/04 11:46:42 AM
MEDICAL OFFICER

Wiley Chambers
4/20/04 11:50:58 AM
MEDICAL OFFICER

Brian Harvey
4/20/04 01:38:38 PM
MEDICAL OFFICER

Jonca Bull
4/20/04 03:50:53 PM
MEDICAL OFFICER

3/1/04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-640

ISTA Pharmaceuticals, Inc.
Attention: Marvin J. Garrett
V.P. Regulatory Affairs, Quality & Compliance
15279 Alton Parkway, Suite 100
Irvine, California 92618

Dear Mr. Garrett:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vitrase (hyaluronidase for injection).

We also refer to the teleconference meeting between representatives of your firm and the FDA on February 13, 2004. The purpose of the meeting was to further discuss labeling for this pending NDA.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

MEETING MINUTES

Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products

MEETING DATE: February 13, 2004

TIME: 12:30 PM EST

APPLICATION: NDA 21-640

MEETING TYPE: Guidance meeting on labeling

DRUG: Vitrase (hyaluronidase for injection)

SPONSOR: ISTA

FDA PARTICIPANTS:

Lori Gorski, Project Manager
Wiley Chambers, Deputy Director
William Boyd, Medical Officer
Jennifer Harris, Medical Officer
Raphael Rodriguez, Project Manager
Michael Puglisi, Project Manager
Zhou Chen, Pharm/Tox Reviewer
Linda Ng, Chemistry Team Leader
Nancy Halonen, Project Manager
Carmen DeBellis, Chief Project Manager

INDUSTRY PARTICIPANTS:

Vince Anido, PhD, President and CEO, ISTA
Marvin Garrett, VP, Regulatory Affairs, Quality & Compliance
Lisa R. Grillone, PhD, VP, Clinical Research & Medical Affairs
Bill Craig, VP Product Research
Tom Mitro, VP Sales and Marketing
Mahshid Zahed, Director Quality Assurance
George Baklayan, Assistant Director Analytical Development
Tara Craven, Regulatory Consultant
Jean Siegel, Regulatory Consultant
Cynthia Hartsen, Regulatory Assistant

MEETING OBJECTIVES: Guidance meeting on labeling and packaging issues for the drug product.

BACKGROUND INFORMATION: Hyaluronidase has been on CDER's drug shortage list for more than 2 years.

QUESTIONS

1. We understand the Agency prefers that the product be identified as "hyaluronidase." Our previous understanding was that "ovine" would be included in the identification. Is that acceptable or why has this changed?

***Division Response:** The product should follow the USP monograph nomenclature, hyaluronidase for injection. If in the future the USP monograph changes, your product name will have to change also.*

2. We understand that the Agency considers the use of Sterile Water for Injection as an alternative for reconstitution of Vitrase. Wydase is reconstituted with Sodium Chloride for Injection. In addition, all data submitted to the Vitrase NDA have been based upon the use of Sodium Chloride for Injection and not Water for Injection. The USP monograph for Hyaluronidase for Injection does not provide instructions for reconstitution so that does not appear to be the source of this alternative diluent. We would appreciate knowing why the Agency wants to add this alternative.

Division Response: *The division does not have a preference for reconstitution with water or with sodium chloride for injection. We do however require that the label be consistent with what you have previously used.*

3. We understand that the Agency would like to refer to the contents of the vial as 6200 USP units and we would like to know how this figure was derived. _____
- _____
- _____

4. Please comment on why the Agency does not consider new information that pertains to the mechanism of action of hyaluronidase and animal pharmacokinetic data to be relevant to the hyaluronidase API and finished product.

Division Response: *New information that is necessary for the safe and effective use of the product for the approved indications should be included in the labeling; otherwise, it should be deleted.*

5. Please comment on why the Agency does not consider the large body of clinical evidence that the ISTA studies represent, including safety experience in terms of adverse reactions, to be relevant to a prescribing physician.

Division Response: *The agency considers all information about the drug product when reviewing the labeling. Statements which would potentially confuse a physician or encourage off label use are not included.*

6. What is the basis for the statement that furosemide, benzodiazepines, and phenytoin have been found to be incompatible with hyaluronidase?

Division Response: *This information was identified during a search on published literature studies.*

7. Please comment on why the Agency does not consider a statement regarding single use of a vial and the fact that Vitrase contains no preservatives to be relevant information for a prescribing physician.

Division Response: *It is relevant information and may be included.* _____

8. We understand that the Agency would like to change the pregnancy category from C —
What is the basis for this change?

Division Response: *The basis of this change is adequate and well controlled studies in the literature regarding the clinical use in pregnant women.*

9.

10.

11.

Division Additional Comments

The following paragraph should be inserted between the second first and second paragraph of the Clinical Pharmacology section:

Hyaluronidase cleaves glycosidic bonds of hyaluronic acid and, to a variable degree some other acid mucopolysaccharides of the connective tissue. The activity is measured in vitro by monitoring the decrease in the amount of an insoluble serum albumen-hyaluronic acid complex as the enzyme cleaves the hyaluronic acid component.

The Division noted no other specific comments.

Minutes created by Lori Gorski, Project Manager

{See appended electronic signature page}

Wiley Chambers, M.D.
Deputy Director

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/s/

Wiley Chambers
3/1/04 11:09:58 AM

2/25/04

MEMORANDUM OF TELECON

DATE: February 9, 2004

APPLICATION: NDA 21-640

BETWEEN:

Name: Marv Garrett
949-788-5303
ISTA Pharmaceuticals, Inc.

AND

Name: Lori M. Gorski, Project Manager
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550

SUBJECT: Granting Type C NDA labeling meeting for Vitrase (hyaluronidase for injection)

A meeting request was submitted on February 6, 2004, asking for dialogue on draft labeling received from the Division on NDA 21-640, Vitrase (hyaluronidase for injection). They provided questions via e-mail. A teleconference has been scheduled for Friday, February 13, 2004, at 12:30 PM.

On February 9, 2004, the sponsor was notified by e-mail of the date of the proposed meeting. The sponsor has accepted the date for their meeting.

See electronic signature page

Lori M. Gorski
Project Manager

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/s/

Lori Gorski

2/25/04 08:56:47 AM

meeting granted on 2/9/04 and held on 2/13/04



NDA 21-640

DISCIPLINE REVIEW LETTER

ISTA Pharmaceuticals, Inc.
Attention: Marvin J. Garrett
V.P. Regulatory Affairs, Quality & Compliance
15279 Alton Parkway, Suite 100
Irvine, California 92618

Dear Mr. Garrett:

Please refer to your August 4, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vitrase (hyaluronidase for injection).

Our preliminary reviews of the Clinical and Chemistry, Manufacturing and Controls sections of the application have identified the following deficiencies:

Clinical

1. The application does not contain an assessment of the potential to cause allergic reactions. A clinical trial that establishes the level of allergic reactions resulting from use of this product should be conducted. This can be established by studying a representative population of patients using a skin test by means of an intradermal injection of approximately 0.1 mL (15 U) of a 150 Units/mL solution to determine if the level of allergic reactions is less than

Chemistry

2. The hyaluronidase activity acceptance criterion should comply with the current USP monograph for Hyaluronidase for Injection. Please revise the acceptance criterion to no less than the labeled potency. The potency should be 6200 USP Units/vial. Please submit the revised drug product specification, stability protocol, and labeling to reflect this change.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response,

and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Wiley Chambers
2/4/04 10:32:48 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-640

ISTA Pharmaceuticals, Inc.
Attention: Marvin J. Garrett
V.P. Regulatory Affairs, Quality & Compliance
15279 Alton Parkway, Suite 100
Irvine, California 92618

Dear Mr. Garrett:

Please refer to your August 4, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vitrase (hyaluronidase for injection).

On December 5, 2003, we received your December 4, 2003, major amendment to this application. The receipt date of this submission is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 5, 2004.

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Lori Gorski

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Lori Gorski has signed for Carmen DeBellas

16 page(s) have been
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and/or confidential
information that is not
disclosable.

(b4)

Date: January 15, 2004

From: Wiley A. Chambers, MD
Deputy Director, Division of Anti-Inflammatory, Analgesic and Ophthalmologic
Drug Products, HFD-550

Through: Brian Harvey, MD, PhD _____
Acting Division Director, Division of Anti-Inflammatory, Analgesic and
Ophthalmologic Drug Products, and Deputy Director, Office of Drug Evaluation V

Through: Jonca Bull, MD _____
Director, Office of Drug Evaluation V

The hyaluronidases are a family of β , 1-4 endoglucosaminidases that depolymerize hyaluronic acid (HA) and chondroitin sulfate. The drug products are partially purified preparations usually sourced from mammalian testicular tissue. The family of hyaluronidase products has never been fully characterized. After multiple discussions within the Center for Drug Evaluation and Research, the following recommendations have been established.

Sodium hyaluronidase is always administered and acts with a co-administered product. The co-administered product is another drug product, when hyaluronidase is used as an adjuvant to increase the absorption and dispersion of other injected drugs; the co-administered product is parental fluid in hypodermoclysis; the co-administered product is a radiopaque product when hyaluronidase is used as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.

The action of hyaluronidase to cause the hydrolysis of hyaluronic acid, a viscous mucopolysaccharide which seems to bind water in the interstitial tissues and act as a physical barrier to the invasion of foreign substances that has been known since the 1940's.¹ Clinical efficacy of hyaluronidase is based on the ability to break down (depolymerize) HA in the body, thereby allowing the co-administered product to flow into the tissue.

The drug product hyaluronidase was named hyaluronidase (versus the original name of _____) because it breaks down hyaluronic acid (HA). The USP assay for the potency of hyaluronidase for injection is a direct in vitro measurement of the ability to depolymerize HA. Standardized HA is used in the test. The action to depolymerize HA and act as a spreading agent, along with the correlation to the USP test has been demonstrated or described in multiple clinical study publications which include:

¹ JAMA, September 20, 1949. Volume 135, No. 3, p. 160-161. Submitted to NDA 6-343.

1. Hechter, O et al. The Clinical Use of Hyaluronidase in Hypodermoclysis. J Pediatrics. 1947; 30(6):645-656. (submitted to NDA 6-343)
2. Cella LJ, Means JA. Clinical Significance of Hyaluronidase. Marquette M Review. 1947; 13:14-18. (submitted to NDA 6-343)
3. Hyaluronidase (The Spreading Factor) in Hypodermoclysis. JAMA, 1947; 135(5):289. (submitted to NDA 6-343)
4. The Biologic Significance of Hyaluronidase. JAMA, 1947; 135(3): 160-161. (submitted to NDA 6-343)
5. Hechter O, Dopkeen SK, Yudell MH. The Clinical Use of Hyaluronidase in Hypodermoclysis. J Pediatrics, 1947; 30(6): 645-656. (submitted to NDA 6-343)
6. Hechter O. Reconstitution of the Dermal Barrier to Fluid Diffusion Following administration of Hyaluronidase. Proc Soc Exp Biol Med. 1948; 67: 343-344. (submitted to NDA 6-343).

Hyaluronidase is administered to the local site where the product is expected to act.² There are no issues of distribution or bioavailability because of the local administration. The expected pharmacologic action is immediate (within a minute) of contact. The potency of the product is determined using a controlled amount of substrate. Since the USP test is a direct measure of the substrate, HA being broken down in the body and the drug product being administered locally, the test is an appropriate surrogate for clinical efficacy. The standardization of the test provides an acceptable mechanism for determining the efficacy of the drug product. The labeled amount of hyaluronidase is expressed in the drug product packaging in USP units utilizing this assay.

Safety

Hyaluronidase injection and hyaluronidase for injection have been safely used and marketed for over 50 years with millions of uses per year. The safety of different formulations and sources of hyaluronidase is described in the literature from the 1940s through 2003 (including cattle, sheep, horse, rabbit, human, recombinant human). Additionally, a review of adverse events for hyaluronidase products from different formulations and different sources has demonstrated very few adverse events. In the case of products with their own clinical studies or marketing history, evaluations of the clinical studies and the adverse events from the marketing history of that particular product have demonstrated similar results.

The benefit to risk ratio is supported by conclusions reached during the DESI evaluation with the expectation that the allergic reaction rate would not exceed an incidence of — in the general population. The indicated uses include use as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. The most frequently reported adverse experiences have been a lack of effectiveness of the co-administered product. It is not possible to determine whether that lack of effect is due to the hyaluronidase or the co-administered drug product. The next most common events are local injection site reactions. Hyaluronidase has also been reported to enhance the adverse events associated with co-administered drug products.

² Swinyard EA, Pathak MA. Surface-Acting Drugs. In: Goodman AG, Gilman LS, Rall TW, Murad F eds. The Pharmacological Basis of Therapeutics. Seventh Edition, MacMillan Publishing Company 1985.

In addition to the years of marketing experience and studies in the United States, ten (10) years of foreign post-marketing information exists for a product marketed in the United Kingdom. The reported safety profile is consistent with the current labeling of the approved Wydase product.

The inability to completely characterize hyaluronidase leads to an inability to verify that the allergic reaction rate of the product proposed for marketing is less than the allergic reaction rate for a less purified product (10% incidence in the general population).³ For hyaluronidase products without human exposure or when a change in the source or manufacturing process occurs, the potential for immunogenicity is recommended to be evaluated using either a dosing regimen as indicated for the proposed indications of hyaluronidase or a skin test utilizing an intradermal injection of approximately 0.1 mL (15 U) of a 150 USP Unit/mL in at least 30 healthy subjects. Thirty subjects, in this case are only acceptable, if there are no allergic reactions observed in the thirty subjects. If an allergic reaction is noted, additional subjects would need to be evaluated to assure that the 95% confidence interval of the event rate is less than 10%. Because there is a chance of a reaction occurring, even if unlikely, it is highly recommended that the study be conducted in more than 30 individuals. The table below identifies the number of positive reactions which could occur in a given set of subjects, yet still maintaining an adverse reaction rate of less than 10%:

<u>Number tested</u>	<u>Maximum number of reactions</u>
30 subjects	No reactions
31 or more subjects	1 reaction or less
50 or more subjects	2 reactions or less
67 or more subjects	3 reactions or less
83 or more subjects	4 reactions or less
98 or more subjects	5 reactions or less
169 or more subjects	10 reactions or less
236 or more subjects	15 reactions or less
300 or more subjects	20 reactions or less

Allergic reactions, if they occur, would be expected to occur local to the site of administration within 20 minutes of administration of the drug product.

Summary:

While the extensive literature available for hyaluronidase products establishes a good base for safety and efficacy of hyaluronidase drug products, the following additional tests are considered clinically necessary anytime the source or manufacturing process changes because the drug product cannot be fully characterized:

1. Efficacy should be confirmed by a determination of potency utilizing the USP monograph test for hyaluronidase.
2. Safety should be confirmed by the monitored administration of the drug product in its proposed final form to individual subjects in a manner that establishes that the 95% confidence interval of the expected allergic reaction rate is less 10%.

³ Schwartzman J, Levbar M. Hyaluronidase: Further Evaluation in Pediatrics. J Pediat. 1950; 36: 79-86.

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/s/

Wiley Chambers
1/26/04 08:31:36 AM
MEDICAL OFFICER

Brian Harvey
1/26/04 10:06:52 AM
MEDICAL OFFICER

Jonca Bull
1/27/04 01:18:30 PM
MEDICAL OFFICER

MEMORANDUM

Date: December 24, 2003

To: Brian Harvey, M.D., Ph.D.
Deputy Director, Office of Drug Evaluation V, HFD-105
Acting Director, Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products, HFD-550

Lori M. Gorski
Project Manager, Division of Anti-Inflammatory, Analgesic, and
Ophthalmologic Drug Products, HFD-550

From: Charles E. Lee, M.D.
Medical Officer, Division of Pulmonary and Allergy Drug Products,
HFD-570

Through: Badrul A. Chowdhury, M.D., Ph.D.
Director, Division of Pulmonary and Allergy Drug Products, HFD-570

Subject: Medical officer consultation regarding clinical data necessary to support
the safety of hyaluronidase products

Materials: Citizen Petition, Baxter Healthcare Corporation
FDA Docket 2003P-0494, 10/27/03
Draft Clinical Review of Citizen's Petition
W. A. Chambers, MD, 11/18/03
Clinical Team Leader Memorandum, Hyaluronidase NDAs
W. Boyd, M.D., 12/19/03

1. EXECUTIVE SUMMARY

The Office of Drug Evaluation V (ODE V) and the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (DAAODP) have consulted the Division of Pulmonary and Allergy Drug Products (DPADP) on safety issues related to hypersensitivity reactions to hyaluronidase.

Although the hyaluronidase applications reference the DESI notices, support for safety from clinical data for the specific product should be provided for products with no marketing history anywhere in the world. If the product is approved in other countries, support for safety should include postmarketing data for the specific product from those countries. Additional clinical data addressing the immunogenicity of the product is also recommended.

If the product has been marketed for a long period and where a reasonable amount of clinical data exist, a small open label clinical study of 100 to 200 patients is recommended to address immunogenicity. If the foreign postmarketing data are robust, they may be adequate to support safety, and a clinical study may not be necessary. Skin tests and samples for in vitro evaluations of hyaluronidase-specific IgE are recommended prior to and after administration of the product. The latter recommendation is based on the assumption that such in vitro tests of hyaluronidase-specific IgE already exist or can be easily developed. Skin tests would be preferable, because it may be immunologically very difficult to test for all epitopes of this varied protein mix in an in vitro assay. Furthermore, information gathered from skin tests would be more practical to apply in a clinical setting.

For products that have no clinical or postmarketing data, the amount of additional clinical data required to assess safety and immunogenicity will be greater. In this circumstance, it may be necessary to conduct an open-label study large enough to rule out a frequency of serious immediate hypersensitivity reactions of 0.5 to 1.0%. All patients should be skin tested prior to administration of the product and serum should be drawn at baseline prior to treatment and frozen. The frequency of immediate hypersensitivity reactions should be assessed and patients who have immediate hypersensitivity reactions should be re-skin tested at a reasonable time after the reaction, perhaps within 1 to 2 months. We recommend that serum samples also be drawn at the same time and paired with the baseline serum samples to be assayed for hyaluronidase-specific IgE using in vitro assays.

Spontaneous reports of immediate hypersensitivity reactions to the product should be monitored in the post-approval period, regardless of the amount of existing clinical and postmarketing data at the time of approval. We recommend that in the post-approval period, the applicant perform skin testing and in vitro testing of a defined number of patients who have immediate hypersensitivity reactions to the product.

2. BACKGROUND

The Office of Drug Evaluation V (ODE V) and the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (DAAODP) have consulted the Division of Pulmonary and Allergy Drug Products (DPADP) on safety issues related to hypersensitivity reactions to hyaluronidase. DAAODP currently has four NDAs for hyaluronidase submitted under Section 505(b)(2) of the FD&C Act that reference DESI notices for hyaluronidase. ODE V and DAAODP would like to know what types of clinical data would be necessary to support drug safety for this group of products.

Hyaluronidases are a group of enzymes that depolymerize hyaluronic acid and chondroitin sulfate. The hyaluronidase enzymes have "spreading factor" activity, and increase the ability of toxins or drugs to diffuse through tissue by breaking down hyaluronic acid, a component of the extracellular matrix.¹ Hyaluronidases are produced by pathogenic bacteria such as Streptococci, and are found in a variety of toxic venoms. The enzymes are also produced by various mammalian tissues. Hyaluronidase drug products are mammalian in origin, and generally are derived from bovine or ovine testicular tissue.

Hyaluronidase products have been marketed for more than 50 years, with millions of uses per year. There have been NDAs for ten hyaluronidase products in the past and each of the applicants were permitted to market their products. The most recently marketed approved product, Wydase® (NDA 06-343), was originally marketed by Wyeth. The NDA is now held by Baxter Healthcare Corporation. Marketing of Wydase® was discontinued in 2000, but Baxter Healthcare Corporation is currently working to resume production. The Agency recently determined that the Wydase® product was not withdrawn from sale for reasons of safety or effectiveness and announced that this determination will allow the Agency to approved abbreviated new drug applications (ANDAs) for hyaluronidase for injection [68 FR 62810, November 6, 2003].

Approved indications for Wydase® include use as an adjuvant to increase the absorption and dispersion of other injected drugs, for hypodermoclysis, and as an adjunct in subcutaneous urography for improving resorption of radioopaque agents. The safety and effectiveness of the product was supported by DESI evaluations (DESI 6343, 6714, 7933). Currently, the most frequent use of hyaluronidase is in ophthalmic surgery as an adjunct to use of locally injected anesthetic agents. There is also some use of hyaluronidase in neonates to help speed the absorption of extravasated intravenous fluids.

The originally marketed product had a rate of anaphylaxis that was fairly high, on the order of 10% or so. The older products were less pure than the recently marketed product. As the purity of the product improved, there was a decrease in the frequency of anaphylaxis to less than 1%. Some large published studies have reported a frequency of reported immediate hypersensitivity reactions of less than 0.1%.

A search of AERS with AERS DataMart reveals 189 adverse events reports for Wydase® over the last 30 years. Among these 189 reports there are two reports for anaphylactic or anaphylactoid reactions.

3. SPECIFIC QUESTIONS

ODE V and DAAODP's questions and DPADP's responses follow below.

What clinical data would be necessary to support drug safety for this type of product?

In our opinion, although these applications reference the DESI notices, support for safety from clinical data for the specific product should be provided for products with no marketing history anywhere in the world. The clinical data should be specific for the product that is proposed for marketing, as each hyaluronidase product is likely to be different in terms of origin, purity, and other CMC characteristics and therefore may be different in the potential for immunologic sensitization and immediate hypersensitivity reactions. If the product is approved in other countries, support for safety should include postmarketing data for the specific product from those countries. Additional clinical data addressing the immunogenicity of the product are also recommended.

With those products with a large volume of real world experience, would skin testing be adequate to address the issues of allergic reactions/immunogenicity?

The label for the Wydase® product recommended that patients have skin testing prior to receiving treatment.

_____ Skin testing and in vitro tests of hyaluronidase-specific IgE have been reported to be positive in individuals who have had immediate hypersensitivity reactions to hyaluronidase.^{1,2} The sensitivity, specificity, and positive and negative predictive values of these tests are not known, however.

Skin testing would be an important part of plan to assess the immunogenicity of these products. In the circumstance of a product that has been marketed for a long period and where a reasonable amount of postmarketing data exist, a small clinical study that evaluates immunogenicity may be sufficient to demonstrate that the product is not highly likely to be associated with immediate hypersensitivity reactions. If the foreign postmarketing data are robust, they may be adequate to support the safety of the drug,

and a clinical study may not be necessary. If the postmarketing data are not robust, an open label study of 100 to 200 patients exposed to the drug for the proposed indications may be able to supply the necessary safety information. Patients could have skin tests prior to receiving the drug, as recommended in the labeling for the previously approved product, and could have repeat skin at an appropriate time after administration of the product, perhaps within one to two months. Serum samples could also be drawn prior to administration at the same time to assess the production of hyaluronidase-specific IgE using in vitro techniques such as ELISA, RAST, or IgE-immunoblotting. The recommendation for in vitro tests of hyaluronidase-specific IgE is based on the assumption that such tests already exist or can be easily developed. These data would be valuable in assessing the value and usefulness of these tests in identifying those who may be at risk for an immediate hypersensitivity reaction to the product. Skin testing would be preferable, because it may be immunologically very difficult to test for all epitopes of this varied protein mix in an in vitro assay. Furthermore, information gathered from skin tests would be more practical to apply in a clinical setting.

Consideration should be given to asking to applicant to monitor spontaneous reports of immediate hypersensitivity reactions to the product in the post-approval period. We also recommend that the applicant perform skin testing and in vitro testing of a defined number of patients in the post-approval period who have immediate hypersensitivity reactions to the product. Such information would further define the benefit of these tests.

In products which have no marketing experience/no human data, what types of clinical trial designs would you propose to demonstrate drug safety?

The amount of additional clinical data required to assess safety and immunogenicity will be greater for these products than for products that have existing data. In this circumstance, it may be necessary to conduct an open-label study large enough to rule out a frequency of serious immediate hypersensitivity reactions of 0.5 to 1.0%. We would recommend that all patients should be skin tested prior to administration of the product and that serum should be drawn at baseline prior to treatment and frozen. The frequency of immediate hypersensitivity reactions should be assessed and patients who have immediate hypersensitivity reactions should be re-skin tested at a reasonable time after the reaction, perhaps within 1 to 2 months. We would recommend that serum samples should also be drawn at the same time and paired with the baseline serum samples and assayed for hyaluronidase-specific IgE using in vitro assays.

We would recommend that spontaneous reports of immediate hypersensitivity reactions to these products in the post-approval period should also be monitored. As we recommended for hyaluronidase products that have clinical data, consideration should be given to skin testing and in vitro testing of a defined number of patients in the post-approval period who have immediate hypersensitivity reactions to the product.

4. REFERENCES

1. Szepefalusi Z, et. al. Eur J Pediatr. 1997; 156(3): 199-203.
2. Agarwal A, et. al. Anaesthesia. 2003; 58(8): 814-815.

Reviewed by:

Charles E. Lee, M.D.

Medical Officer, Division of Pulmonary and Allergy Drug Products

Badrul Chowdhury, M.D., Ph.D.

Director, Division of Pulmonary and Allergy Drug Products

cc: Division File, NDAs 06-343, — 21-640, —
HFD-105/Harvey/Deputy Office Director
HFD-550/Gorski/Project Manager
HFD-105/Bull/Office Director
HFD-550/Chambers/Deputy Division Director
HFD-550/Boyd/Medical Team Leader
HFD-102/Meyer/Office Director
HFD-570/Chowdhury/Division Director
HFD-570/Sullivan/Deputy Division Director
HFD-570/Gilbert-McClain/Medical Team Leader
HFD-570/Barnes/CPMS
HFD-570/Lee/Medical Reviewer

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/s/

Charles Lee
12/29/03 10:00:31 AM
MEDICAL OFFICER

Badrul Chowdhury
12/29/03 10:30:59 AM
MEDICAL OFFICER
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		Clinical Pharmacology & Biopharmaceutics (HFD 860/870/880) Tracking/Action Sheet for Formal/Informal Consults																												
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Background This is a 505(b)(2) application for Vitrace® (ovine hyaluronidase). The proposed indication for Vitrace® is as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis (subcutaneous administration of fluids); and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. Dosing ranges from up to 150U for use in hypodermoclysis to 75U for subcutaneous urography. Hyaluronidase (previously marketed as Wydase®) is considered by the FDA to be a medically necessary drug product and is currently on FDA's list of drug shortages because it is no longer manufactured by Wyeth Laboratories. The Vitrace® formulation differs from the Wydase® formulation only in that it is of ovine origin and is preservative-free. This proposed formulation would provide a safe, consistent and reliable supply of this product as an alternative to the existing supply, which is provided by compounding of bovine hyaluronidase by individual pharmacies.																														

Drug Substance

Wydase®, the original Wyeth product (NDA 6-343) was approved in March 1950 and was subject to the Drug Efficacy Study Implementation or DESI review and was found to be effective for the indications in a FR notice published 9/23/70 (vol. 35, no. 185, pg. 14800-801. Wydase® itself was a less purified form of hyaluronidase from bovine testicular protein. The ovine form of hyaluronidase differs in amino acid sequence, protein structure; carbohydrate analysis and enzyme function from the bovine hyaluronidase. The active ingredient in Vitrase® is a preparation of highly purified ovine (sheep) testicular protein enzyme hyaluronidase. Ovine hyaluronidase occurs in two natural forms, α - and β -hyaluronidase. In addition to the active ingredient, the drug substance contains two other proteins as impurities, _____ Vitrase® is provided as a lyophilized powder in a preservative-free formulation.

The exact chemical structure of the enzyme is unknown. Even so, the following range of molecular weights were calculated: _____ Daltons (Da) for α -hyaluronidase, _____ Da for β -hyaluronidase, _____

Both the α - and β - forms of ovine hyaluronidase are active. When forms are purified to greater than _____ purity, they have very similar specific activities of _____

Each vial of _____ of ovine hyaluronidase contains 5mg lactose, 1.92mg potassium phosphate dibasic, and 1.22 potassium phosphate monobasic. Each 0.05mL contains _____ of hyaluronidase for injection.

Waiver Request

The current NDA submission contains no in vivo biopharmaceutic information. ISTA Pharmaceuticals is requesting a waiver of in vivo bioequivalence studies based on the fact that there are no existing stocks of Wydase® available for use as a comparator.

While the lack of a comparator is a problem it is not a valid reason for a waiver of in vivo biostudies under 21CFR320. However, grounds for a waiver do exist in that there is not a chemical assay for hyaluronidase and the exact chemical structure is unknown. As it is, the chemical extraction/purification of hyaluronidase from ovine testicles consists of a multiple series of precipitations and acid-base rinses resulting in a "purified" protein extract. This extract is then put through a USP potency test which is based on the amounts of tyrosine present and is thus an indirect measure of hyaluronidase content.

Labeling

The current proposed package insert while providing information on the in vitro activity of the enzyme does not provide any information as to the quantification of enzyme activity. The following paragraph should be inserted between the second first and second paragraph of the Clinical Pharmacology section:

Hyaluronidase cleaves glycosidic bonds of hyaluronic acid and, to a variable degree, some other acid mucopolysaccharides of the connective tissue. The activity is measured in vitro by monitoring the decrease in the amount of an insoluble serum albumen-hyaluronic acid complex as the enzyme cleaves the hyaluronic acid component.

Recommendation

Given the fact that this product is considered by the FDA to be a medically necessary drug and that it is indicated for only very special situations at low doses, a waiver of in vivo biostudies under the "good cause" provisions of 21CFR320.22(e)

Date _____

SIGNATURE OF REVIEWER: _____	Date _____
SIGNATURE OF TEAM LEADER: _____	
CC.: HFD # [880]; TL: [Selen]; DD: [Lazor]	Project Manager: _____ Date _____

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Dennis Bashaw
11/24/03 11:47:33 AM
BIOPHARMACEUTICS

Arzu Selen
11/24/03 12:09:44 PM
BIOPHARMACEUTICS

NDA 21-640, VITRASE® (Ovine Hyaluronidase) for Injection, 6200 USP Units/vial

This CMC review of the Carton and Container Mock-Ups and Package Insert plus two issues raised during the May 4, 2004 VITRASE review team meeting about review #2, will be added as a memo to review # 2 already entered in DFS.

Amendment of March 23, 2004

The lettering for the storage conditions in the 100% mock-up for the immediate container is illegible. It was recommended that the storage temperatures be removed and to add, a "protect from light" statement. The intention was to free some space so as to have larger letters.

Amendment of March 30, 2004

ISTA made the recommended changes to the immediate container. The letters are somewhat larger but it is still difficult to read.

VITRASE review team Meeting

On May 4, 2004 there was a meeting for the whole team reviewing this NDA. In this meeting changes were recommended for the immediate container, carton and Package Insert.

The change for both the immediate container and the carton was to add the source of the hyaluronidase. The suggestion was to add "Lyophilized, Ovine" Under the USP name (Hyaluronidase for Injection) and leave a space in between the two lines.

For the Package Insert one of the changes was to add the same statement, "Lyophilized, Ovine" under the USP name (Hyaluronidase for Injection).

In the "Description Section", the issue of whether the pH should be a range rather than a single target number was resolved by the fact that to include a pH range, would be akin to disclosing proprietary information.

Issues raised during the meeting about review # 2.

The issue of the USAN name was not very clear in review # 2. On November 12, 2003, the CMC review team was consulted by USAN about several proposed names for hyaluronidase drug substance. The purpose was to treat this enzyme in the same manner as the insulins from the naming point of view. On November 26, 2003, the team recommended the name "Hyaluronidase (source to be indicated as ovine on labeling). On February 25, 2003, this name became official for the USAN.

In review # 2, two USP monograph proposals by ISTA were discussed. One was a new monograph for their ovine hyaluronidase drug substance and the second one was for updating the existing monograph for the Hyaluronidase for Injection drug product. A question about the status of these monographs was raised.

Amendment of May 4, 2004.

ISTA agreed to the changes requested by The Agency and submitted the revised Package Insert, immediate label and carton in this amendment.

Comment: All outstanding issues with respect to the Package Insert, immediate label and carton have been resolved satisfactorily in this portion of the review. All other issues were resolved in reviews #1 and #2. Review #2 contains the recommendation for approval.

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ON ORIGINAL**

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/s/

Libaniel Rodriguez

5/5/04 01:13:46 PM

CHEMIST

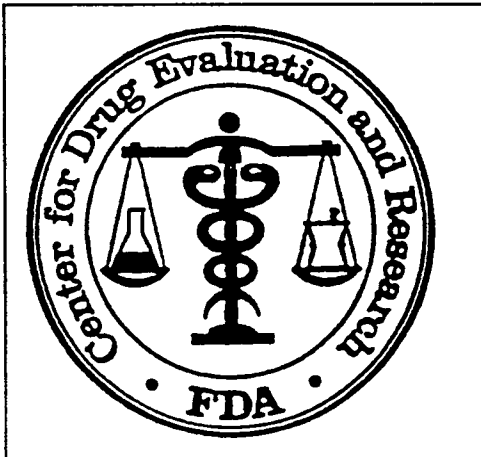
Approval, this is an addendum to review #2

Norman Schmuff

5/5/04 03:06:30 PM

CHEMIST

**.FACSIMILE TRANSMISSION
RECORD**



From: Libaniel Rodriguez, Ph.D.
Review Chemist

Division of Anti-Inflammatory, Analgesic
and Ophthalmic Drug Products
HFD-550

Phone 301-827-2069
Fax 301-827-2531

Date: October 6, 2003

To: Name: Marvin J. Garrett
Company: ISTA Pharmaceuticals
City: Irvine State:CA
Phone #: 949 788 5303

FAX #: 949 788 6013

Number of Pages (INCLUDING COVER PAGE):

Please telephone (301) 827-2069 IMMEDIATELY if re-transmission is necessary.

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Should you have any questions about this information request please call me.

Please respond by October 10, 2003 or before.

Libaniel Rodriguez

NDA 21-414 Vitrase® (ovine hyaluronidase)

CMC COMMENTS

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

1. Please tighten the acceptance criterion for hyaluronase activity in the drug product specification sheet. Based on the updated stability data, we suggest a value of _____

2. Correct Typos under "Analysis Procedure" in the drug product specification sheet for Bacterial Endotoxins and Sterility.
3. Revise and submit Specification Sheet for drug product.
4. The primary stability protocol for drug product is missing a commitment statement under the "Deviations and Investigations" section, about deviations from the approved acceptance criteria (See "Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics", February 1987, Page 4).
5. Please revise and submit the drug product primary stability protocol to include the revised hyaluronase activity and the statement above.

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/s/

Libaniel Rodriguez
10/6/03 09:17:42 AM
CHEMIST
IR

Linda Ng
10/6/03 10:23:04 AM
CHEMIST
No action needed by PM

CONSULTATION RESPONSE
Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED:
August 15, 2003

DESIRED COMPLETION DATE: September 15, 2003
PDUFA DATE: October 4, 2003

ODS CONSULTS #:
02-0200-1

TO: Lee Simon, MD
Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
HFD-550

THROUGH: Lori Gorski, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products
Regulatory Project Manager
HFD-550

PRODUCT NAME:
Vitrase
(Ovine Hyaluronidase for Injection)
— USP units/vial

NDA SPONSOR:
ISTA Pharmaceuticals Inc.

NDA # 21-640

SAFETY EVALUATOR: Scott Dallas, R.Ph.

SUMMARY: In response to a consult from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550), the Division of Medication Errors and Technical Support (DMETS) conducted a re-review of the proposed proprietary name, "Vitrase", to determine the potential for confusion with approved proprietary and established names as well as pending names. The proposed container labels, carton and package insert labeling was reviewed in an attempt to focus on safety issues to prevent possible medication errors.

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Vitrase.
2. DMETS recommends the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550) consult with the CDER Labeling and Nomenclature Committee (LNC) for the proper nomenclature of the established name.
3. DMETS recommends implementation of the labeling revisions outlined in Section III to encourage the safest possible use of this product.
4. DDMAC finds the proprietary name, Vitrase, acceptable from a promotional perspective.

/S/

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax (301) 443-9664

/S/

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Parklawn Building Room 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: September 22, 2003
NDA NUMBER: 21-640
NAME OF DRUG: Vitrase
(Ovine Hyaluronidase for Injection)
— USP units/vial
NDA SPONSOR: ISTA Pharmaceuticals Inc.

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (DAAODP) for a reassessment of the proposed proprietary name Vitrase.

Subsequent to this action the sponsor submitted a new drug application, NDA# 21-640 to support the indications of Vitrase as an adjuvant to increase the absorption and dispersion of other injected drugs, hypodermoclysis, and as an adjunct in subcutaneous urography.

Additionally, the sponsor revised the package insert labeling to only address the indications submitted in NDA# 21-640. The labels and labeling submitted with this application were reviewed.

PRODUCT INFORMATION

Vitrase is the proposed name for ovine hyaluronidase. It is a preparation of highly purified ovine testicular hyaluronidase. Hyaluronidase hydrolyzes hyaluronic acid by splitting the glucosaminidic bond. This temporarily decreases the viscosity of the cellular cement and promotes diffusion of injected fluids and thus can aid in their absorption. Therefore, Vitrase is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs. It is also indicated for hypodermoclysis, and as an adjunct in subcutaneous urography.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to "Vitrase" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system (TESS) was conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Vitrase". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel did not identify any additional proprietary or established names that have the potential for confusion with "Vitrase".

¹ MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, 2003, Facts and Comparisons, St. Louis, MO.

³ The Drug Product Reference File [DPR], the DMETS database of proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/main/trademarks.htm>

⁵ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

2. DDMAC did not have any concerns with the promotional aspects of the name, "Vitraser".
3. DMETS' Phonetic Orthographic Computer Analysis (POCA) database was unavailable to search at the time of this review.

B. SAFETY EVALUATOR RISK ASSESSMENT

1. Re-review of Proprietary Names identified in ODS Consult # 02-0200

DMETS conducted a re-review of the proprietary names and product characteristics previously identified for the potential to cause confusion with Vitraser. The proprietary names, AMO Vitrox, Ultraser, Viokaser, Vitrasert, Altaser, and Vitravene were identified as possessing the potential to sound-alike and/or look-alike to Vitraser. DMETS conducted the analysis because this application has included additional indications for use, a route of administration (subcutaneous) and usual dosages (75 USP units or 150 USP units).

Upon review of these additional characteristics, DMETS concludes these additional characteristics did not increase the potential risk of a medication error between the proposed product Vitraser and the other products. No additional overlapping characteristics were identified in the analysis of Vitraser and the other products.

2. Review of the comments from the DAAODP

DMETS reviewed comments submitted by the Division concerning their assessment of the three proprietary names, Vitrasert, Vitravene, and AMO Vitrox that DMETS concluded had a potential for confusion with Vitraser.

The comments were provided as an excerpt from a March 28, 2003 memo from the Division Deputy Director.

DMETS appreciates the opportunity to receive comments and feedback from the Division concerning our consults. Upon review of the Division's comments, DMETS concurs with the rationale that there is a low potential risk for an administration error to occur between Vitraser and the products, Vitrasert and Vitravene. Vitrasert is an implant, an uncommon dosage formulation and Vitravene has a very limited and specialized distribution in the U.S. with an expected distribution of less than 100 units for 2003. However, we disagree with the Divisions' rationale concerning AMO Vitrox and Vitraser. DMETS is still concerned with the potential for confusion between these proprietary names, especially due to the potential for the names to sound-alike and look-alike.

DMETS is especially concerned with the potential for name confusion and medication errors between Vitraser and AMO Vitrox, if Vitraser is approved with the indication for use and route of administration. DMETS would like the Division to consider the following information regarding the potential for confusion between the names Vitraser and AMO Vitrox. First, the prefix "AMO" is included as part of the proprietary name for AMO Vitrox. DMETS does not know what information the prefix "AMO" is suppose to convey to healthcare professionals. However, DMETS notes that AMO Vitrox is marketed by Advanced Medical Optics (AMO). Thus, we assume that AMO is an acronym for the company. On September

17, 2003 a search of the AMO website identified two references to Vitrax. One reference pertained to sodium hyaluronate solution and the other reference was presented on the web site as follows:

vitrax®, an eye drop solution, may be prescribed by your physician. It is specifically used for the treatment of itching associated with seasonal allergic conjunctivitis - the allergic response to pollens and molds. And by controlling the itch, vitrax® helps stop the cycle of itching and rubbing that may lead to substantial eye irritation. vitrax® Solution is available in a convenient plastic bottle with a controlled-dropper tip.
(<http://www.amo-inc.com/site/products/consumers/overview.asp?id=vitrax&largeText=>)

A representative for Advanced Medical Optics indicated that they were not familiar with Vitrax (as an eye drop solution). DMETS notes that inaccurate information only increases the potential for confusion. Additionally, when looking up the name Vitrax in the 2003 Redbook, the proprietary name is listed alphabetically in the letter 'V' section as "Vitrax (AMO)". Products containing hyaluronate are not listed in the Orange Book, therefore the proprietary name AMO Vitrax is also not listed. Practitioners are more likely to ignore a suffix or prefix if it is not required to differentiate products with the same root tradename or if it does not provide some distinguishing characteristic (e.g., dosage form) of the product. Therefore, DMETS would consider it common practice for practitioners to refer to AMO Vitrax simply as Vitrax.

Without the prefix AMO, the proprietary names Vitrax and Vitrase have the potential to sound-alike and like-alike. As noted in the original review, Vitrase can sound similar to Vitrax, since both names begin with "Vitra". The "x" sound in Vitrax can also sound similar to the "se" sound in Vitrase, especially if interpretation occurs over the telephone. When scripted the names can look similar, since the first five letters, "Vitra", of each name are the same. Also the letter "x" in Vitrax and the letters "se" in Vitrase may be difficult to distinguish, depending on how the letters are scripted. Generally, scripted trailing letters that are found on written prescriptions are harder to differentiate. A handwriting sample is included for review.

Vitrax Vitrase

Also, if the established name is not clearly written or pronounced, name confusion could occur since the established names are similar, hyaluronate sodium vs. hyaluronidase. For example, if sodium hyaluronate and ovine hyaluronidase are abbreviated to hyaluronate and hyaluronidase, then it may be difficult to distinguish which product is prescribed. Additionally, the products could be stored near each other (by proprietary or established name). In a hospital setting, these products may be kept as floor stock items in the operating room, etc. Thus, there is the potential for selection errors at the pharmacy level and in the operating room, etc. Moreover, the packaging configuration of Vitrax may contribute to name confusion. Vitrase (NDA# 21-640) will be packaged as a single-use vial:

Vitrax is packaged as an individual syringe with a cannule (per DAOCDDD Deputy Division Director). Although, the products are packaged in 3 different configurations, all three are injectables that will be stored near each other, which increases the potential for confusion. The similarities in names,

settings of use (inpatient), and the fact that both products are injectables increases the opportunity for name confusion between Vitrax and Vitrase.

Post-marketing experience has shown healthcare professionals can administer a product by the wrong route of administration. On May 7, 2003 a search of the FDA Drug Quality Reporting System detected 94 reports of medications administered by the wrong route. A January 1999 newsletter from the Institute for Safe Medication Practices (ISMP) alerted practitioners to the danger of preparing oral solutions. The article stated,

"Many healthcare practitioners we speak with believe that the administration of oral products IV would not occur in their institution since it appears to be such a flagrant practitioner knowledge deficit. However, based on the number of reports we have received, it is not an extremely rare occurrence."

Based on DMETS post-marketing experience, DMETS is concerned that Vitrase and Vitrax (both parenteral dosage formulations) could be administered by the wrong route.

DMETS is also concerned if the name Vitrase is approved for the indications for use and route of administration as indicated in NDA# 21-640, then the likelihood of confusion will increase with verbal and oral communication between the names Vitrase and Vitrax.

DMETS still has questions concerning the dose and administration of Vitrase as presented in the package insert labeling for NDA# 21-640. For example, the route of administration and detailed administration directions are not stated in the section titled "Absorption and Dispersion of other Injected Drugs". This section also does not state the actual dose that should be administered to various groups of patients (adolescents, children, etc). Therefore, DMETS cannot completely evaluate the potential of similar or other overlapping features with the numeric portion of the dose or if the unit of measure, mL could appear in the dosing of Vitrax and Vitrase.

3. The Established Name

The sponsor has proposed that the established name be presented as (Ovine Hyaluronidase) Lyophilized. First, DMETS is concerned if different mammalian sources of this soluble enzyme product could potentially cause allergic reactions. If so, DMETS questions how the mammalian source of this soluble enzyme product should be noted on this and other hyaluronidase products. Secondly, the term "lyophilized" does not represent a dosage formulation in the Dosage and Formulation section of the CDER Data Standards Manual. DMETS recommends the Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products (HFD-550) consult with the CDER Labeling and Nomenclature Committee (LNC) for the proper nomenclature of the established name.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

DMETS reviewed the revised container label, carton and package insert labeling in an attempt to focus on safety issues to prevent possible medication errors. The revised label and labeling only represented information that will appear on the label and labeling, but they were not copies of an actual label or labeling. DMETS has identified

the following areas of possible improvement in the interest of minimizing user error and maximizing patient safety.

A. General Comment:

1. DMETS recommends the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products consult with the CDER Labeling and Nomenclature Committee (LNC) to determine the proper designation of the established name. DMETS has questioned if the mammalian source of the soluble enzyme product should be part of the established name or follow the presentation of the established name. DMETS also questioned the proper presentation of the dosage formulation in the established name. The sponsor should revise the presentation of the established name on all labels and labeling based on the LNC recommendation.

2. _____

B. Container Label

1. _____
2. _____
3. _____
4. _____

C. Carton Labeling

1. _____
2. _____

D. Package Insert Labeling

1. _____

a. The Directions for Reconstitution Subsection

i.

ii.

iii.

iv.

b. The Absorption and Dispersion of Injected Drugs Subsection

i.

ii.

iii.

iv.

v.

vi.

vii.

c. The Hypodermoclysis subsection

i.

ii.

2. How Supplied Section

IV. RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Vitrase.
2. DMETS recommends the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550) consult with the CDER Labeling and Nomenclature Committee (LNC) for the proper nomenclature of the established name.
3. DMETS recommends implementation of the labeling revisions outlined in Section III to encourage the safest possible use of this product.
4. DDMAC finds the proprietary name, Vitrase, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

/S/

Scott Dallas, R.Ph.
Safety Evaluator
Office of Drug Safety (DMETS)

/S/

Concur:

Denise Toyer, Pharm.D.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Scott Dallas
10/2/03 08:45:06 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
10/2/03 02:46:47 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
10/2/03 03:52:53 PM
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-640

ISTA Pharmaceuticals, Inc.
Attention: Marvin J. Garrett
V.P. Regulatory Affairs, Quality & Compliance
15279 Alton Parkway, Suite 100
Irvine, California 92618

Dear Mr. Garrett:

Please refer to your August 4, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vitrase (ovine hyaluronidase).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on October 4, 2003, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Lori Gorski

9/30/03 09:54:17 AM

Lori Gorski has signed for Carmen DeBellas



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-640

ISTA Pharmaceuticals, Inc.
Attention: Marvin J. Garrett
V.P. Regulatory Affairs, Quality & Compliance
15279 Alton Parkway, Suite 100
Irvine, California 92618

Dear Mr. Garrett:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Product: Vitrase (ovine hyaluronidase)

Review Classification: Priority

Date of Application: August 4, 2003

Date of Receipt: August 5, 2003

Our Reference Number: NDA 21-640

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 4, 2003, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, call Lori M. Gorski, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Carmen DeBellas, R.Ph.
Chief, Project Management Staff
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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/s/

Lori Gorski

8/11/03 03:37:03 PM

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